

Application No.: 10/615,809

Attorney Docket No. A-817 (US)

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ARGUMENT

(1) Claims 5-7 and 9 stand rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819), Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137)). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

(2) Claim 31 stands rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137)). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

(3) Claims 30 and 34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176) and In re Wood (199 USPQ 137)). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

**I. The Examiner Has Failed To Establish A Prima Facie
Case Of Obviousness In Relation To Claims 5-7 and 9**

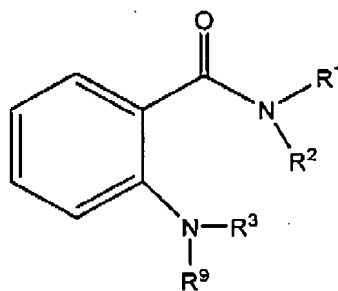
The Examiner has rejected claims 5-7 and 9 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819), Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137)).

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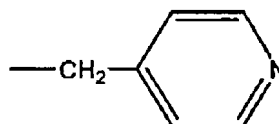
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Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 5 line 7, to page 7 line 12. Specifically, in attempting to support the rejection the Examiner notes that examples 2.39 and 2.56 of Huth et al.



disclose compounds of the formula



where R² and R⁹ are hydrogen, R³ is —CH₂—, and R¹ is indol-5-yl, or 4-chloropyridyl. Then the Examiner asserts that:

"Patani et al. teach ring replacements of NH for CH₂ in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles, as well as quinoline/isoquinoline, equivalent structures."

(Final Office Action at page 6 lines 12-14). The Examiner then proceeds to assert that:

"Fotouhi et al. teach that substituting and [sic] 2,3-dihydro-1H-indole for indole give [sic] molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2."

(Final Office Action at page 6 lines 15-17). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teachings of both Patani and Fotouhi far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that

* Appellants question the inclusion of judicial decisions, such as In re Wood, as prior art references. While the holdings of judicial precedent can certainly be relied upon to support the underlying rationale of a rejection, the

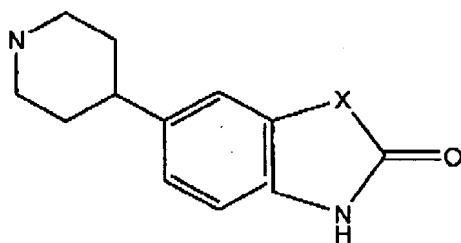
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any and all "replacements of NH for CH₂ in aromatic and aliphatic rings"[†] will **always** provide "equivalent" structures, with "equivalent" properties relative to **any and all** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad overarching trends across diverse scaffolds and biologic targets, as a gross oversimplification.

The Examiner's ultimate conclusion that Patani et al establish the equivalency of all 5-yl and 6-yl indoles under all circumstances is not even supported by the cited text of the reference (i.e., page 3158-3159). A review of the actually cited pages reveals a disclosure of 2 separate chemical scaffolds that both employ certain **5-yl** indolinone-type fragments (see e.g., Figure 34 (compound 52), and Figure 36). Each of these compound is distinct in both structure and chemical activity.

The first cited scaffold in Patani (Figure 34, compound 52) discloses a genus of **PDE III modulators** of the following formula::



X = CH₂, NH

This genus covers both

- (1) piperadin-5-yl, 2,3-dihydro benzimidazolones; and
- (2) piperadin-5-yl, indoline -2-one

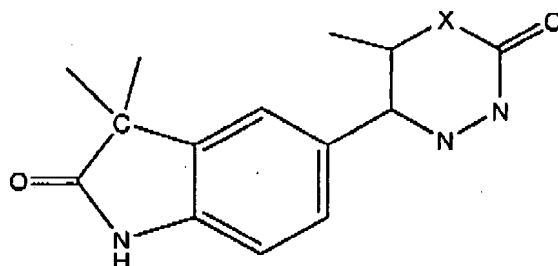
The cited scaffold thus encompasses only **5-yl** substituted 2,3-dihydrobenzimidazolones/ or indolinones

judicial decision itself does not appear to be properly categorized as "prior art".

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The second cited scaffold in Patani (Figure 36, compound 54) disclose a genus of Cardiotonic agents of the following formula:



Like the previously cited scaffold, this second scaffold also encompasses only 5-yl substituted 2,3-dihydrobenzimidazolones/ or indolinones

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents at the 5 position of the cited scaffolds in Patani.
- The cited compounds are all 5-yl substituted indolinone compounds. The Examiner does not provide any rational for the implicit equation of indoles and indolinones.
- Contrary to the Examiner's position, the cited reference does not disclose any purported equivalency between either 5-yl or 6-yl indoles. Indeed, the reference only discloses 5-yl substituted indolinones. How the Examiner now draws a conclusion as to the universal equivalency of any and all corresponding 6-yl isomers, is beyond Appellants comprehension.
- The Examiner does not explain how Patani's disclosure of certain PDE III modulators in Figure 34, and other structurally distinct

[†] Appellants note this NH could not be substituted with CH₂ in aromatic systems without violating rules of

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Cardiotonic agents in Figure 36, would lead any person of skill in the art to reasonably expect that certain fragments of the scaffold could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

Moreover, the Examiner has not explained how a person of skill in the art, reviewing Fotouhi's disclosure (which relates to ICAM inhibitors of a structurally distinct scaffold), would conclude that the substitution of 2,3, dihydro-1-H indole for indole -- on the completely different kinase inhibitor scaffold covered by the claims on appeal -- would be expected to yield compounds of similar properties. The Advisory Action indicates that this rejection has been maintained because:

"Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

First: Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets than VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors).

II. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claim 31

The Examiner has rejected claim 31 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137).

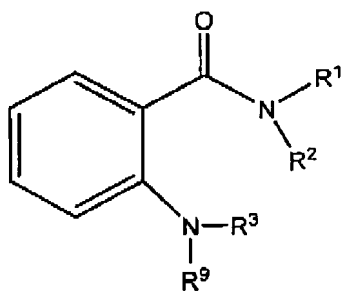
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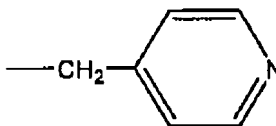
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Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 10 line 3, to page 11 line 12. Specifically, in attempting to support the rejection the Examiner notes that example 2.56 of Huth et al. discloses a



compound of the formula



where R² and R⁹ are hydrogen, R³ is , and R¹ is indol-5-yl. Then the Examiner asserts that:

"Patani et al. teach ring replacements of NH for CH₂ in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles equivalent structures."

(Final Office Action at page 10 lines 17-19). The Examiner then proceeds to assert that:

"Fotouhi et al. teach that substituting and [sic] 2,3-dihydro-1H-indole for indole give [sic] molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2."

(Final Office Action at page 11 lines 1-3). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teachings of both Patani and Fotouhi far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that **any** and all "replacements of NH for CH₂ in aromatic and aliphatic rings" will **always** provide "equivalent" structures, with "equivalent" properties relative to **any and all**

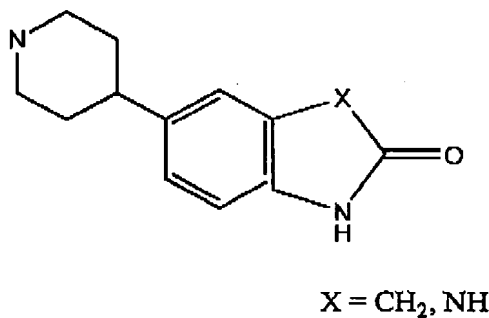
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biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad overarching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplification.

The Examiner's ultimate conclusion that Patani et al establish the equivalency of all 5-yl and 6-yl indoles under all circumstances is not even supported by the cited text of the reference (i.e., page 3158-3159). A review of the actually cited pages reveals a disclosure of 2 separate chemical scaffolds that both employ certain 5-yl indolinone-type fragments (see e.g., Figure 34 (compound 52), and Figure 36). Each of these compound is distinct in both structure and chemical activity.

The first cited scaffold in Patani (Figure 34, compound 52) discloses a genus of **PDE III modulators** of the following formula:



This genus covers both

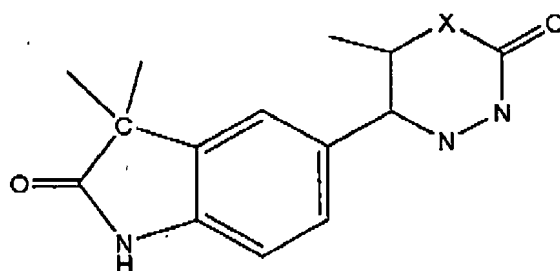
- (1) piperadin-5-yl, 2,3-dihydro benzimidazolones; and
- (2) piperadin-5-yl, indoline -2-one

The cited scaffold thus encompasses only **5-yl** substituted 2,3-dihydrobenzimidazolones/ or indolinones

The second cited scaffold in Patani (Figure 36, compound 54) disclose a genus of **Cardiotonic agents** of the following formula:

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Like the previously cited scaffold, this second scaffold also encompasses only 5-yl substituted 2,3-dihydrobenzimidazolones/ or indolinones

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents at the 5 position of the cited scaffolds in Patani.
- The cited compounds are all 5-yl substituted indolinone compounds. The Examiner does not provide any rational for the implicit equation of indoles and indolinones.
- Contrary to the Examiner's position, the cited reference does not disclose any purported equivalency between either 5-yl or 6-yl indoles. Indeed, the reference only discloses 5-yl substituted indolinones. How the Examiner now draws a conclusion as to the universal equivalency of any and all corresponding 6-yl isomers, is beyond Appellants comprehension.
- The Examiner does not explain how Patani's disclosure of certain PDE III modulators in Figure 34, and other structurally distinct Cardiotonic agents in Figure 36, would lead any person of skill in the art to reasonably expect that certain fragments of the scaffold could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

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Moreover, the Examiner has not explained how a person of skill in the art, reviewing Fotouhi's disclosure (which relates to ICAM inhibitors of a structurally distinct scaffold), would conclude that the substitution of 2,3, dihydro-1-H indole for indole – on the completely different kinase inhibitor scaffold covered by the claims on appeal – would be expected to yield compounds of similar properties. The Advisory Action indicates that this rejection has been maintained because:

"Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

First: Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors)

III. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claims 30 and 34

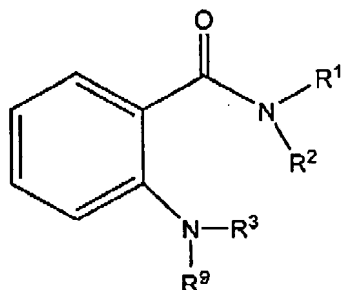
The Examiner has rejected claim 30 and 34 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176) and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 8 line 11, to page 9 line 19. Specifically, in attempting to

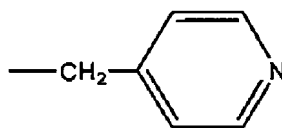
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support the rejection the Examiner notes that example 2.49 of Huth et al. discloses a



compound of the formula



where R² and R⁹ are hydrogen, R³ is , and R¹ is 7-1,2,3,4-tetrahydroquinolyl. Then the Examiner asserts that:

“Patani et al. teach ring replacements of NH for CH₂ in aromatic and aliphatic rings. See pages 3158-3159. This would make pyridine/pyrimidine, as well as quinoline/isoquinoline equivalent structures.”

(Final Office Action at page 9 lines 9-11). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teaching of both Patani far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that *any* and all “replacements of NH for CH₂ in aromatic and aliphatic rings” will *always* provide “equivalent” structures, with “equivalent” properties relative to *any and all* biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-arching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplification.

The Examiner's ultimate conclusion that Patani et al establish the equivalency of all pyridine/pyrimidine and quinoline/isoquinoline under all circumstances is not even supported by the cited text of the reference (i.e., page 3158-3159). A review of the

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actually cited pages reveals that (1) while some diverse scaffolds do employ pyridine fragments no chemical scaffolds are disclosed that employ pyrimidine fragments; and (2) while one scaffold discloses a specific antibacterial scaffold employing certain quinolone and isoquinolone fragments, the references discloses no scaffolds encompassing quinoline and isoquinoline fragments. How the Examiner makes the logical leap establishing the equivancy of quinolones/quinolines and isoquinolones/isoquinolines, is beyond Appellants' comprehension.

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents required in the cited scaffolds in Patani.
- The cited compound only disclose specific quinolone and isoquinolone compounds. The Examiner does not provide any rational for the implicit equation of of these compounds to the structurally distinct quinoline and isoquinoline compounds covered in the claims pending on appeal.
- The Examiner does not explain how Patani's disclosure of certain antibacterial quinolones and isoquinolones, would lead any person of skill in the art to reasonably expect that quinoline and isoquinoline fragments employed in the distinct the scaffold covered in the claims on appeal could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

The Advisory Action indicates that this rejection has been maintained because:

"Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

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The Advisory Action indicates that this rejection has been maintained because:

"Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

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IV. The Teaching of Patani

Applicants respectfully submit that the Examiner has interpreted the teaching of Patani et al. far too broadly, and that a fair consideration of this reference does not actually provide anywhere near the absolute concrete guidance on equivalency that has been proposed by the Examiner. Indeed, a review of the pages of Patani et al. specifically cited by Examiner reveals that this disclosure does not even encompass topics such as the substitution of pyrimidine for pyridine, or the substitution of isoquinoline for quinoline. Rather, these pages disclose, *at best*, that:

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- (1) in relation to antihistamine effect, certain pyridines and phenyls can be employed to obtain active compounds (see Figure 31 at p. 3158),
- (2) in relation to antibacterial effect, certain quinilones and isoquinolones can be employed to obtain active compounds (see Figure 38 at p. 3159); and
- (3) in relation to certain PDE III modulator scaffolds certain 2,3-dihydrobenzimidazolone fragments can be substituted for indolinone fragments.

The other ring systems discussed at pages 3158-3159 of Patani et al., do not even approach structural similarity between pyridines/pyrimidones or quinolines/isoquinolines. The Examiner's belief that this disclosure of Patani et al. clearly establishes that any substitution of N for CH in any aromatic systems (or NH for CH₂ in any non-aromatic systems) will always result in compounds of equivalent activity in all targets, is simply an overreaching interpretation that is not supported by the disclosure itself. Indeed Patani et al. specifically note that:

- "The concept of bioisosterism is often considered to be qualitative and intuitive." (Patani et al. at page 3147), rather than the facile, precise, all-encompassing generalizations than have been put forth by the Examiner.
- The substitutions discussed in the reference only represent *potential* for producing compounds of similar activity. (See page 3148: "Thus, an additional objective of this review was to demonstrate *the opportunities* that one has in employing bioisosteres" (emphasis added); and "Bioisosteric replacements of functional groups ... have enhanced *the potential* for the successful development of new clinical agents" (emphasis added); See also page 3158: "Classical isosteric substitutions when applied within ring systems result in different heterocyclic analogues which *can be* effective bioisoteres."). Thus, it is clear that Patani et al. do not

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purport to endorse the type of broad interpretation that has been set forth by the Examiner, in an attempt to support this rejection. At best, Patani et al. provide a suggestion to try isosteric substitutions in order to find bioisosteric equivalents in relation to certain targets. Patani, et al. do not even attempt to suggest that such substitutions will always work in any target at issue.

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The Examiner's extremely overbroad interpretation of Patani et al. represents the very foundation of the obviousness rejections. The failure of the Patani reference to actually suggest the propositions set forth by the Examiner, dooms the remainder of the analysis to failure.

CLAIMS 37-45

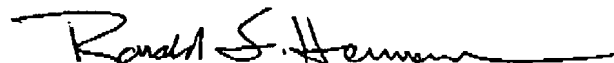
Method of treatment claims 37-45 were canceled in Applicants' response to the Final Action as being drawn to an unelected invention group. Applicants wish to point out that these claims are properly subject to rejoinder upon the determination of patentability of the pending claims.

CONCLUSION

Based on the above observations and arguments, Appellants respectfully request that the Examiner withdraw the rejections of record and pass the pending claims to allowance.

Respectfully submitted,

Dated: June 20, 2007



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